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Title

The Presence of Co-morbid Mental Health Problems in a Cohort of Adolescents with Chronic Fatigue Syndrome (CFS)

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Conflicts of Interest

TC is the author of several self-help books on chronic fatigue. KR has co-authored a book with TC called "Overcoming Chronic Fatigue in Young People".

Title

The Presence of Co-morbid Mental Health Problems in a Cohort of Adolescents with Chronic Fatigue Syndrome (CFS)

Abstract

Objective: To report on the prevalence of mental health disorders in adolescents with chronic fatigue syndrome (CFS), and to compare the diagnoses identified by a brief clinician administered psychiatric interview with self-report screening questionnaires.

Design: Cross-sectional study.

Setting: Consecutive attenders to specialist CFS clinics in the UK.

Patients: N = 52 Adolescents, age 12-18 with CFS.

Measures: Self-report questionnaires and a brief structured psychiatric diagnostic interview, administered by an assistant psychologist.

Results: On the psychiatric interview, 34.6% met a diagnosis of major depressive disorder, and 26.9% had an anxiety disorder. Of these, fifteen percent had co-morbid anxiety and depression. Those with a depression diagnosis reported significantly greater interference on the school and social adjustment scale. They also scored significantly higher on trait anxiety, but not on state anxiety. There were no differences between those who had an anxiety disorder and those who did not on fatigue, disability or depressive symptoms. Children's

Depression Inventory (CDI) score was associated with a depression diagnosis on the psychiatric interview. However, neither the state nor the trait subscale of the State-Trait Anxiety Inventory (STAI) were associated with an anxiety diagnosis.

Conclusions: Clinicians should assess for the presence of anxiety and depressive disorders in adolescents with CFS using a validated psychiatric interview. Treatment should be flexible enough to accommodate fatigue, depression and anxiety. Transdiagnostic approaches may suit this purpose. Goals should include pleasurable activities particularly for those who are depressed.

Introduction

Chronic Fatigue Syndrome (CFS) is characterised by "*persistent or debilitating fatigue that is not lifelong, the result of ongoing exertion, alleviated by rest, explained by other conditions and that results in a substantial reduction in activity"* (NICE, 2007). In children, fatigue needs to have lasted for at least 3 months to make a diagnosis. Additional symptoms include general malaise, headaches, muscle and joint pain, sore throats, cognitive problems, nausea and sleep disturbance. Prevalence rates range from 0.06 to 2.4% (Chalder, Goodman, Wessely, Hotopf, & Meltzer, 2003; Crawley et al., 2012; Haines, Saidi, & Cooke, 2005; Nijhof et al., 2011).

CFS has a considerable impact on functioning. Children who attend specialist services miss, on average, 1 year from school as a result of their illness (Rangel, Garralda, Levin, & Roberts, 2000). One study reported that 62% attended school less than 40% of the time, and 28% did not attend school at all (Crawley & Sterne, 2009).

Children with CFS appear to experience considerable rates of co-morbid mental health problems. However, most studies have used self-report questionnaires as tools for detecting distress. Estimates of the prevalence of comorbid depression vary considerably between 17% (Nijhof et al., 2013) and 42% (Walford, Nelson, & McCluskey, 1993), most likely as a result of differences in sampling strategies, cut-offs for identifying depression and study settings. Estimates of the prevalence of anxiety have also varied; up to 38% of teenage girls with CFS are

reported to have high levels of anxiety, with lower levels in boys (Crawley, Hunt, & Stallard, 2009).

Using self-report questionnaires has drawbacks. The questionnaires most commonly used include items such as restlessness, lack of energy and fatigue which may be confounded with CFS. It is assumed that the scales are sensitive and specific when used with adolescents with CFS but this has not been examined.

Few studies have used psychiatric interviews designed to identify and diagnose mental health problems in children with CFS, despite this being the most robust means of detecting such difficulties (NICE, 2015). In an opt-in hospital sample of 28 children, the KSADS psychiatric interview identified that 8 participants (29%) met the diagnostic criteria for depression and 7 (25%) met the criteria for an anxiety disorder (Garralda & Rangel, 2005). However, this study of limited generalisability due to the sampling strategy and small sample size. The Development and Well-being Assessment (DAWBA) was used in a cross-sectional population study to examine the association between psychiatric disorders and fatigue syndromes. Anxiety but not depression was associated with chronic fatigue and CFS (Chalder et al., 2003). In a prospective study using the DAWBA, anxiety or depression at time 1 was associated with increased risk of fatigue 4-6 months later (Rimes et al., 2007). However, in these studies there were no paediatrician confirmed CFS diagnoses of fatigue, and inconsistencies between

parental report of fatigue and those who met the diagnostic criteria for fatigue. Furthermore, the number of participants meeting the CFS diagnosis was very small.

The current study examined the prevalence of mental health problems in a cohort of adolescents consecutively referred to a specialist CFS service using a structured psychiatric interview. The research questions were (1) What is the prevalence of mental health disorders in paediatric CFS? (2) Do those with a diagnosis of depression or anxiety differ from those who are not depressed or anxious? and (3) Do screening questionnaires distinguish between those who are depressed and anxious and those who are not?

Method

Participants

Consecutive clinic attenders at two specialist CFS Units from August 2010 to December 2012 were invited to participate. 89young people attended an initial assessment during the recruitment period. Of these, 63 had a confirmed diagnosis of CFS. Full data, including at least some sections of the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID) were available for 52 (82.5%) of CFS patients. Independent samples t-tests showed that these patients did not differ significantly from those with CFS who did not complete the MINI-KID in terms of age ($t(82) = 0.159$, $p = .874$), fatigue ($t(78) = -.524$, $p = .602$), physical functioning on the SF36PFS ($t(71) = -.576$, $p = .566$), or school attendance ($t(70)$

= -.760, p = .450). The group who did not complete the MINI-KID were significantly more impaired on occupational functioning on the School and Social Adjustment Scale (t (76) = 2.131, p = .036).

Measures

Psychiatric Diagnoses - The Mini International Neuropsychiatric Interview for Children and Adolescents, MINI-KID (Sheehan et al., 1998), is a structured diagnostic schedule, which covers 20 psychiatric diagnoses from the DSM-IV in a relatively brief time, taking an average of 34 minutes to administer (Sheehan et al., 2010). The MINI-KID has demonstrated good concurrent validity when compared to the gold standard psychiatric interview, the Kiddie Schedule for Affective Disorders and Schizophrenia (Sheehan et al., 2010) and substantial to excellent inter-rater and test-retest reliability. A researcher was trained by a Clinical Psychologist to administer the MINI-KID. The researcher scored the MINI-KID, and the coding was subsequently checked by a Research Assistant (SA) and, independently checked by a Clinical Psychologist with considerable experience of working in child mental health (ML).

Demographic information and background characteristics, including school attendance, were collected within routine clinical practice.

Young people completed the following measures, which are all reliable and valid:

Fatigue – Chalder Fatigue Questionnaire (Chalder et al., 1993). This 11 item scale assesses fatigue severity, both mental and physical. Each item is rated on a 4 point scale with a recall period of 1 month.

Physical Impairment/Disability - Short Form 36 (SF-36) physical functioning scale (McHorney, Ware Jr, & Raczek, 1993). The 10 item physical function scale lists activities of daily living such as 'climbing one flight of stairs' and asks respondents, on a 3 point scale, to rate how much their health limits them in these activities.

Participation in Life – The 5 item Work and Social Adjustment Scale, WSAS (Mundt, Marks, Shear, & Greist, 2002) instructs respondents to rate the extent to which their problem interferes with their ability to undertake work, domestic, social and leisure activities and how it affects their close relationships. In this context "work" was replaced by "school or college" to ensure its appropriateness for adolescents.

Anxiety – The State Trait Anxiety Inventory, STAI (Speilberger, Gorsuch, & Lushene, 1970), is a 40 item scale which measures the intensity of felt anxiety, both state anxiety (temporary, experienced in particular situations) and trait anxiety (a general tendency to perceive situations as threatening). Each item is rated on a 1-4 scale.

Depression – The Children's Depression Inventory, CDI (Kovacs, 1992) is a 27 item self-report scale, which asks about the presence of depressive symptoms over the past 2 weeks. Responses are rated on a 0-2 scale.

Procedure

As part of routine clinical practice, questionnaires were sent to all patients to complete and return prior to the initial hospital assessment, together with an invitation letter regarding the use of this data for audit and potential research purposes. At the appointment, patients and their parents were given information sheets and consent forms and the study was explained to them by the assessing clinician. Informed consent was sought from potential participants who were ≥ 16 years old, with consent given by parents for assenting participants who were < 16 years old. The MINI-KID interview was administered after the clinical assessment.

Ethical Approval

This study was approved by an NHS research ethics committee (LREC, ref 08/H0807/107), and the Research and Development departments at the Institute of Psychiatry, South London and Maudsley NHS Trust, and Great Ormond Street Hospital.

Data Analysis

Data was analysed using SPSS 23.0. Incomplete cases were excluded analysis by analysis. Descriptive statistics were conducted to describe the sample. To compare those who met

diagnoses of depression and anxiety on the MINI-KID to those who did not, independent samples t-tests were conducted. Homogeneity of variance was assessed by Levene's Test for Equality of Variances. Where $p < .05$, equal variance was not assumed, and a correction for unequal variance was applied. Binomial logistic regression was conducted to examine the extent to which the questionnaire scores were associated with the MINI-KID diagnostic classifications of depression and anxiety. Cox & Snell R^2 and Nagelkerke R^2 are reported.

Results

The sample consisted of 52 adolescents, age 12 to 18, who met the NICE criteria for CFS (NICE, 2007) based on clinician judgement. Of these, 42 (80.7%) met the Oxford Criteria for CFS (Sharpe et al., 1991). Characteristics of the participants are shown in table 1.

[insert table 1 about here]

Diagnoses on the MINI-KID are shown in table 2. Twenty two (47.8%) of the 46 participants for whom complete data was available did not meet any anxiety disorder or depressive disorder diagnoses. Eighteen (34.6%) of the 52 participants met a diagnosis of major depressive disorder; of these, 12 had recurrent depression, 4 had past depression, 1 had current depression, and 1 had past and current depression. An additional 2 participants met the criteria for dysthymia. Fourteen (26.9%) participants had an anxiety disorder, with 1

participant having 2 co-morbid anxiety disorders. For those with complete data (N = 46), 9 (19.6%) had depression only, 8 (17.4%) had an anxiety disorder only, and 7 (15.2%) had co-morbid anxiety and depression.

[insert table 2 about here]

No participants had alcohol or substance dependency, conduct disorder, oppositional defiant disorder, Tourette's Syndrome or transient tic disorder. One participant had ADHD (inattentive type). In 6 cases (11.5%), it was unclear as to whether the participant may meet the diagnostic criteria for Pervasive Developmental Disorder (PDD), with 42 participants deemed not to meet the PDD criteria.

There was a trend for those who were depressed to be more fatigued (table 3). Those who were depressed reported significantly more interference on the school and social adjustment scale. However, they were not significantly different in terms of percentage school attendance and were not more physically disabled (SF-36). Those who were depressed scored significantly higher on trait anxiety on the STAI but not on state anxiety.

Those who met criteria for an anxiety disorder on the MINI-KID were not significantly different from those who did not on fatigue, disability or depressive symptoms (see table 3). Their

school attendance was considerably lower than those without an anxiety disorder, although this did not reach significance.

[insert table 3 about here]

CDI score was significantly associated with a diagnosis of depression on the MINI-KID, accounting for between 47 and 65% of the variance (χ^2= 29.38, p < .000, R^2 = .472 - .645). CDI score correctly predicted 89% of not depressed cases, and 65% of depressed cases. The addition of disability (WSAS and SF36), anxiety (STAI state and trait) and fatigue (CFQ) as covariates explained 27%-37% of the variance in block 1, with the addition of CDI score in block 2 increasing this to 65%-89% of the variance in block 2, suggesting that CDI score is the best predictor of a depression diagnosis amongst the variables measured (χ^2= 41.93, DF 6, p < .0005, R^2 = .649 - .885).

Previous studies using the CDI in adolescent CFS samples have applied a clinical cut-off of > 15 (Nijhof et al., 2013). In the current study, 32.6% of participants scored >15. Seventy one percent of these also met the diagnostic criteria for depression on the MINI-KID, and 90% of those who were not depressed scored ≤ 15 on the CDI. Ten percent of non-depressed participants scored >15 on the CDI (false positives). Twenty-nine percent of depressed patients did not score > 15 on the CDI (false negatives).

[insert table 4 about here]

Those who met the criteria for an anxiety disorder on the MINI-KID did not differ significantly from those who did not on the STAI. Neither STAI anxiety state score nor STAI trait anxiety score was found to be significantly associated with a diagnosis of anxiety on the MINI-KID (χ^2= .176, DF 2, $p < .916$, $R^2 = .004 - .006$), see table 5.

[insert table 5 about here]

Discussion

In these adolescents attending a specialist CFS unit, one third were found to have depression and a quarter to have an anxiety disorder on a structured psychiatric interview. Fifteen percent of the sample had both depression and anxiety. Those who were depressed rated themselves as significantly more impaired on the school and social adjustment scale. They also scored significantly higher on trait anxiety, but not on state anxiety. There were no differences between those who had an anxiety disorder and those who did not on fatigue, disability or depressive symptoms. Children's Depression Inventory (CDI) score was associated with a depression diagnosis on the psychiatric interview. However, neither subscale of the State-Trait Anxiety Inventory (STAI) were associated with an anxiety diagnosis.

Depression prevalence in this sample is comparable to the level of depression found in previous studies recruiting adolescents with CFS in specialist services (Bould, Collin, Lewis, Rimes, & Crawley, 2013; Crawley et al., 2009; Garralda, Rangel, Levin, Roberts, & Ukoumunne, 1999). This study also highlighted generalised anxiety disorder (GAD) as the most common anxiety disorder. Previous studies reported social anxiety and separation anxiety as being more common (Crawley et al., 2009) but this may be the result of relying on self-report questionnaires. However, it may also be the result of overlapping diagnostic constructs, with social anxiety being a facet of a broader generalised anxiety factor (Whitmore, Kim-Spoon, & Ollendick, 2014).

Having depression appeared to impact on school and social functioning. This highlights how important it is to detect and treat depression in this patient population, who are already likely to miss significant time at school (Crawley & Sterne, 2009; Rangel et al., 2000). Fatigue did not differ significantly between the depressed / non-depressed and anxious / non-anxious groups.

In this cohort of CFS patients, the CDI performed better than in paediatric multiple sclerosis, where only one third of those with depression on the CDI were diagnosed with depression on psychiatric interview (Goretti et al., 2012). Despite this, in the current study, only around two thirds were correctly identified on the CDI as being depressed, indicating that whilst it might be a useful adjunct to a thorough psychiatric assessment, the CDI does not appear to be a convincing screening tool. Furthermore, the STAI was not useful in discriminating anxiety

disorders. This could be because all the participants were relatively anxious, with the no anxiety disorder group containing a lot of subthreshold anxiety, consistent with previous findings of high levels of anxiety in CFS patient samples (Crawley et al., 2009; Garralda & Rangel, 2005). The STAI trait scale also assesses symptoms of depression (Bieling, Antony, & Swinson, 1998), which may explain why those who are depressed scored significantly higher on this measure.

Strengths and Limitations

This study used a structured psychiatric interview to diagnose depression and anxiety. However, the MINI-KID, whilst brief, lacks the depth and flexibility of a diagnostic tool such as the Kiddie Schedule for Affective Disorders and Schizophrenia (KSADS). Diagnostic outcomes on the MINI-KID depend on algorithms and not clinician judgement, and symptoms are rated as present or absent, without further detail regarding severity or frequency. This study was also cross-sectional, which precludes conclusions about causality. As the research assessments were offered to consecutive attenders in routine clinical practice, selection bias would have been reduced. However, the sample was limited to those presenting to specialist services, which is unlikely to represent the full spectrum of adolescents with CFS. Although this study recruited a larger sample than previous studies using diagnostic interviews in paediatric CFS samples, complete data was only available for a subsample of those seen. It is possible that the higher rates of anxiety and depression in CFS reflect the experiences of adolescents with chronic illnesses more broadly, rather than being specific to CFS. This seems unlikely as

previous studies have found that participants with CFS have higher rates of anxiety and depression than those with other chronic illnesses, e.g. migraine (Smith, Martin-Herz, Womack, & Marsigan, 2003) and arthritis (Garralda & Rangel, 2004), and a meta-analysis showed that depressive symptoms appear to be higher in CFS than in other childhood chronic illnesses (Pinquart & Shen, 2011). However, in the current study, the lack of a comparison group precludes definitive conclusions about this.

Implications for Clinical Practice

It is important to assess for comorbid mental health problems in adolescents with CFS who are referred to specialist CFS services. Therefore, healthcare professionals working with adolescents with CFS should routinely assess for anxiety and depression within their clinical interviews, and these could be supplemented with screening tools, although questionnaires that are sufficiently sensitive and specific to enable the detection of anxiety and depression in this population need to be further developed. Where significant anxiety and/or depression is identified, adolescents may need specialist input targeted at mental health problems in addition to treatment for CFS. Furthermore, evidence-based treatments for CFS may need to be modified for those who have co-morbid psychiatric disorders. For example, behavioural activation, in which activities are gradually (re)introduced guided by the individuals' values based goals, has shown promise in adolescents with depression (Orchard et al 2016). Self-report questionnaires should be utilised with caution until their sensitivity and specificity has been established within the patient population of interest.

Conclusions

Adolescents with CFS presenting to a specialist CFS unit had high levels of depression and anxiety diagnoses, consistent with previous research using questionnaires. Depressed adolescents with CFS had greater impairment on the school and social adjustment scale than those without depression.

The CDI was shown to be a potentially useful adjunct to psychiatric assessment, but not necessarily an accurate standalone screening tool for detecting depression. The STAI was not useful in discriminating between those who had an anxiety disorder and those who did not.

Table 1. Characteristics of Participants who completed the MINI-KID

Gender	Male	19 (36.5%)
	Female	33 (63.5%)
Ethnic Origin	White British	46 (88.5%)
	Black British	2 (3.8%)
	Other European	2 (3.8%)
	Black Caribbean	1 (1.9%)
	White Asian	1 (1.9%)

	Range	**Mean (S.D)**
Age (years)	12-18	15.5 (1.72)
Chalder Fatigue Questionnaire	8-33	23.74 (5.48)
Percentage school attendance	0-100	41.63 (36.97)
Duration of illness (months)	5-96	25.26 (19.44)
WSAS Total Score	4-39	23.10 (7.90)
SF-36PFS	0-100	50.98 (25.94)
STAI State Anxiety	26-67	44.21 (11.75)
STAI Trait Anxiety	26-64	43.31 (10.48)
CDI	4-28	13.48 (7.22)

Abbreviations: CDI – Children's Depression Inventory, SF-36PFS – Short Form 36 Physical Function Scale, STAI – State-Trait Anxiety Inventory, WSAS – Work and Social Adjustment Scale

Table 2. Frequency of Diagnostic classifications on the MINI-KID

Diagnostic Classification	Number of participants given diagnosis on MINI-KID (%)	Number of participants not given diagnosis on MINI-KID (%)	Data missing
Major Depression	18 (34.6)	34 (65.4)	0
Panic disorder	4 (7.7)	46 (88.5)	2
Social Phobia	2 (3.8)	48 (92.3)	2
Specific Phobia	2 (3.8)	50 (96.2)	0
Separation Anxiety Disorder	1 (1.9)	50 (96.2)	0
GAD	9 (17.3)	42 (80.8)	2
OCD	0	52 (100)	0
PTSD	0	52 (100)	0
Anorexia Nervosa	1 (1.9)	39 (75)	12
Bulimia Nervosa	0	52 (100)	0

Table 3. Results of independent samples t-tests comparing those who met a diagnosis of depression on the MINI-KID to those who did not, and for those who met a diagnosis of anxiety on the MINI-KID compared to those who did not

Measure		**Mean**	**S.D.**	**SEM**	**t (df)**	***p***	**Mean difference**	**95% CI for mean difference**
DEPRESSION								
CFQ	Depressed	25.76	4.68	1.14	-1.945 (47)	.058	-3.11	-6.32-.11
	Non-depressed	22.66	5.63	.99				
School attendance (%)	Depressed	42.14	43.00	11.49	-.061 (44)	.951	11.98	-24.88-23.41
	Non-depressed	41.41	34.76	6.15				
WSAS	Depressed	26.63	6.31	1.58	-2.265 (47)	.028	-5.23	-9.88- -.58
	Non-depressed	21.39	8.11	1.41				
SF-36	Depressed	48.13	29.99	7.50	.541 (44)	.592	4.38	-11.94-20.69
	Non-depressed	52.50	23.92	4.37				
STAI (state)	Depressed	47.81	12.58	3.14	-1.531 (45)	.133	-5.46	-12.64-1.72
	Non-depressed	42.35	11.05	1.99				
STAI (trait)	Depressed	49.25	10.18	2.54	-3.003 (46)	.004	-8.91	-14.88- -2.94
	Non-depressed	40.34	9.44	1.67				
CDI	Depressed	20.24	5.72	1.39	-6.979 (44)	<.000	-10.72	-13.81- -7.62
	Non-depressed	9.52	4.59	.85				
ANXIETY								
CFQ	Anxiety disorder	22.07	6.72	1.80	1.202 (41)	.236	2.17	-1.48-5.82
	No anxiety disorder	24.24	4.91	.91				
School attendance (%)	Anxiety disorder	55.38	38.00	10.54	-1.465 (38)	.151	-18.90	-45.02-7.22
	No anxiety disorder	36.48	38.33	7.38				
WSAS	Anxiety disorder	23.43	6.86	1.83	-.034 (41)	.973	-.08	-4.99-4.82
	No anxiety disorder	23.34	7.73	1.44				
SF-36	Anxiety	53.48	23.49	6.51	-.693 (39)	.493	-5.96	-23.37-11.45
	No anxiety disorder	47.50	26.55	5.01				
STAI (state)	Anxiety disorder	44.14	12.22	3.27	-.218 (40)	.829	-.821	-8.45-6.81
	No anxiety disorder	43.32	11.18	2.11				
	Anxiety	43.71	11.61	1.86		.836	-.714	-7.65-6.23

STAI (trait)	No anxiety disorder	43.00	10.03	3.10	-.208 (41)			
CDI*	Anxiety	12.92	8.70	2.41	.164 (19.04)	.872	.447	-5.27-6.17
	No anxiety disorder	13.37	6.67	1.28				

Abbreviations: CDI – Children's Depression Inventory, CFQ – Chalder Fatigue Questionnaire, SF-36 – Short Form 36, STAI – State-Trait Anxiety Inventory, WSAS – Work and Social Adjustment Scale

Note: There was homogeneity of variance as assessed by Levene's Test for Equality of Variances for all variables apart from the CDI*, therefore equal variances were assumed for all variables except the CDI, where equal variance was not assumed.

Table 4. Results of binary logistic regression analyses predicting MINI-KID diagnosis of depression versus no depression from CDI score, adjusted for covariates

Step and Variable	β	SE	Wald	DF	P	Exp(B)
Step 1: Covariates						
STAI state anxiety	-1.77	1.32	1.80	1	.180	.17
STAI trait anxiety	.67	.60	1.24	1	.265	1.95
SF36 Physical Functioning	-.11	.10	1.06	1	.304	.90
CFQ total score	-.36	.43	.70	1	.403	.70
WSAS Occupational Functioning	.87	.58	2.31	1	.129	2.40
Step 2: Predictor	4.03	2.83	2.03	1	.155	56.04
CDI score						

Abbreviations: CDI – Children's Depression Inventory, CFQ – Chalder Fatigue Questionnaire, CI – confidence interval; DF – degrees of freedom; Exp(b) – exponentiation of B coefficient or odds ratio, SF-36 – Short Form 36, STAI – State-Trait Anxiety Inventory, WSAS – Work and Social Adjustment Scale

Table 5. Results of binary logistic regression analyses predicting MINI-KID diagnosis of anxiety versus no anxiety from STAI state and trait anxiety scores

Variable	β	SE	Wald	DF	P	Exp(B)
STAI state	.03	.06	.17	1	.677	1.03
STAI trait	-.03	.07	.13	1	.724	.98

Abbreviations: CI – confidence interval; DF – degrees of freedom; Exp(b) – exponentiation of B coefficient or odds ratio, STAI – State-Trait Anxiety Inventory

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